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#14

March 25, 1988

Mr. Ronald Wilson
Office of the Associate Commissioner
for Health Affairs (HFY-20)
Room 11-46
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Novantrone

Dear Mr. Wilson:

Transmitted herewith is a copy of the application for Patent Term Extension of U.S. Patent No. 4,197,249, issued April 8, 1980. The application was filed on February 19, 1988, under Title II of Public Law 98-417, the Drug Price Competition and Patent Term Restoration Act of 1984.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term restoration. Thus, a determination of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 USC 156(d)(2)(A).

This is the second application for patent term extension based on Novantrone. The first application was based on Patent No. 4,278,689 and has been assigned FDA Docket No. 88E-0067.

C.E. Van Horn

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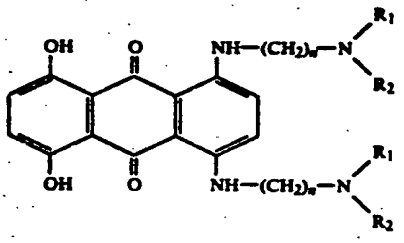
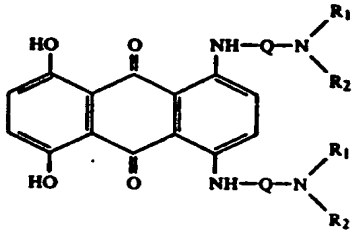


(V)

wherein n is an integer from 2 to 4, inclusive, and R_1 and R_2 are as defined for the preceding preferred embodiment with the proviso that the ratio of the total number of carbon atoms to the sum of total number of oxygen atoms plus the total number of nitrogen atoms in each of the side chains at the 1-position and the 4-position may not exceed four. This preferred embodiment also includes the corresponding leuco bases of the aromatic bases (V), the tautomers thereof, and the non-toxic pharmaceutically acceptable acid-addition salts thereof.

Also embraced within the purview of the present invention are therapeutic compositions of matter useful for ameliorating cancer diseases in mammals and containing certain 5,8-dihydroxy-1,4-bis(substituted-amino)anthraquinones (or the leuco bases and non-toxic acid-addition salts thereof) which may be represented by the following structural formula:



(I)

wherein R_1 is hydrogen or alkyl having from 1 to 4 carbon atoms, R_2 is hydrogen or alkyl having from 1 to 4 carbon atoms, R_1 and R_2 taken together with their associated N(itrogen) is as hereinbefore defined for R_3 and R_4 taken together with their associated N(itrogen), and Q is as hereinbefore defined. This aspect of the invention includes the novel compositions of matter and the method of inducing the regression and/or palliation of leukemia and related cancers in mammals therewith.

The active ingredients of the therapeutic compositions and the novel compounds of the present invention inhibit transplanted mouse tumor growth and induce regression and/or palliation of leukemia and related cancers in mammals when administered in amounts ranging from about 5 mg. to about 200 mg. per kilogram of body weight per day. A preferred dosage regimen for optimum results would be from about 5 mg. to about 50 mg. per kilogram of body weight per day, and such dosage units are employed that a total of from about 350 mg. to about 3.5 grams of the active compound for a subject of about 70 kg. of body weight are administered in a 24-hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that the active compound may be administered in any convenient man-